

## Organic and Biological Chemistry

## Application of the Principle of Hard and Soft Acids and Bases to Organic Chemistry

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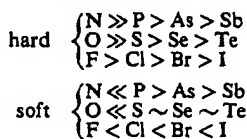
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**Abstract:** The principle of hard and soft acid and bases (HSAB principle) is applied to organic chemistry. Organic molecules are viewed as Lewis acid-base complexes and their relative thermodynamic stability explained in terms of two factors. One is the tendency of intrinsically strong acids to coordinate to the strongest bases. The second is the special stabilization of combinations of hard acids and bases, or soft acids and bases. The symbiotic principle is illustrated, which states that there is an extra stabilization if several soft bases (ligands) or several hard bases cluster about a single acidic atom. The same two principles are applied to rates of nucleophilic and electrophilic substitution reactions in organic chemistry.

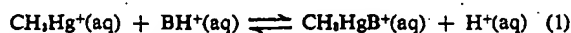
Recently<sup>2</sup> a generalization was proposed which makes it possible to correlate a great many phenomena in various areas of chemistry. Use is made of the concept of generalized, or Lewis, acids and bases. The generalization may be called the principle of hard and soft acids and bases (HSAB). It states that hard acids prefer to coordinate to hard bases and soft acids prefer to coordinate to soft bases.

These terms are qualitatively defined in the following ways: soft base—donor atom is of high polarizability, low electronegativity, easily oxidized, and associated with empty, low-lying orbitals; hard base—donor atom is of low polarizability, high electronegativity, hard to oxidize, and associated with empty orbitals of high energy and hence inaccessible; soft acid—the acceptor atom is of low positive charge, large size, and has several easily excited outer electrons; hard acid—acceptor atom is of high positive charge, small size, and does not have easily excited outer electrons.

Operationally, acids may be defined by following the procedures of Schwarzenbach<sup>3</sup> and Ahrland, Chatt, and Davies.<sup>4</sup> These workers divided metal ions (which are Lewis acids) into two classes called A and B by Schwarzenbach and a and b by Ahrland, Chatt, and Davies. Hard acids follow the same pattern as class a metal ions, and soft acids show the pattern of class b metal ions. For complexes with different donor atoms, the following sequences of stabilities are found.

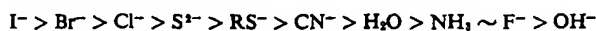


Soft bases might be operationally defined by considering the equilibrium<sup>5</sup>

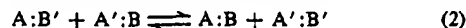


If the equilibrium constant for this reaction is much greater than unity, the base B is soft. If it is near unity, or less than unity, the base is hard. The proton is the simplest hard acid and the methylmercury cation is one of the simplest soft acids. Table I contains a listing of hard and soft bases for later reference.

If the equilibrium constants of eq 1 are used to rank a series of bases, the following order of decreasing softness is obtained.



It turns out that this is not a universal order since a change in one of the reference acids will give a different series. The reason for this may be seen by considering the generalized acid-base exchange reaction.



We expect such a reaction to proceed such that the strongest acid, A, is found coordinated to the strongest base, B. The terms hard and soft do not mean the same as strong and weak. Thus an acid is characterized by at least two properties, its strength and its hardness, or softness; the same is true for a base. It is well known that there is no universal order of acid or base strength; still we recognize that some Lewis acids, such as  $\text{H}^+$ , are much stronger than other acids, such as  $\text{I}_2$ , or that  $\text{H}^-$  is a much stronger base than  $\text{H}_2\text{O}$ . The HSAB principle then states that there is an extra stabilization in  $\text{A}:\text{B}$  if both the acid and base are hard, or if both are soft.<sup>6</sup>

We can usually recognize hardness or softness in a qualitative way by examining an acid or base, particularly the donor or acceptor atoms. The situation may be something like that for the terms solvent polar-

(1) Chemistry Department, Bergen University, Norway. Supported by the Royal Norwegian Council for Scientific and Industrial Research.

(2) R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963); *Science*, **151**, 172 (1966).

(3) G. Schwarzenbach, *Experientia Suppl.*, **5**, 162 (1956); *Advan. Inorg. Chem. Radiochem.*, **3**, 257 (1961).

(4) S. Ahrland, J. Chatt, and N. R. Davies, *Quart. Rev. (London)*, **12**, 265 (1958).

(5) G. Schwarzenbach and M. Schellenberg, *Helv. Chim. Acta*, **48**, 28 (1965); G. Schwarzenbach, *Chem. Eng. News*, **43**, 92 (May 31, 1965).

(6) Thus the equilibrium constant for the reaction  $\text{A} + \text{B} \rightleftharpoons \text{A}:\text{B}$  might be characterized by an equation such as  $\log K = S_A S_B + \sigma_A \sigma_B$ . The factors  $S_A$  and  $S_B$  are strength factors for the acid and base;  $\sigma_A$  and  $\sigma_B$  are softness factors. For a hard acid or base,  $\sigma$  would be negative; for a soft acid or base,  $\sigma$  would be positive; see R. S. Drago and B. B. Wayland, *J. Am. Chem. Soc.*, **87**, 3571 (1965).

Table I. Classification of Bases

Hard	Soft	Borderline
H <sub>2</sub> O, OH <sup>-</sup> , F <sup>-</sup> , CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup> , PO <sub>4</sub> <sup>3-</sup> , SO <sub>4</sub> <sup>2-</sup> , CO <sub>3</sub> <sup>2-</sup> , ClO <sub>4</sub> <sup>-</sup> , NO <sub>3</sub> <sup>-</sup> , ROH, RO <sup>-</sup> , R <sub>2</sub> O, NH <sub>3</sub> , RNH <sub>2</sub> , N <sub>2</sub> H <sub>4</sub>	R <sub>2</sub> S, RSH, RS <sup>-</sup> , I <sup>-</sup> , SCN <sup>-</sup> , S <sub>2</sub> O <sub>3</sub> <sup>2-</sup> , Br <sup>-</sup> , R <sub>3</sub> P, R <sub>3</sub> As, (RO) <sub>3</sub> P, CN <sup>-</sup> , RNC, CO, C <sub>6</sub> H <sub>6</sub> , C <sub>6</sub> H <sub>5</sub> , H <sup>-</sup> , R <sup>-</sup>	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub> , C <sub>6</sub> H <sub>5</sub> N, N <sub>3</sub> <sup>-</sup> , Cl <sup>-</sup> , NO <sub>2</sub> <sup>-</sup> , SO <sub>3</sub> <sup>2-</sup>

ity or electronegativity. These useful concepts lack a precise definition, or rather several definitions exist to suit various kinds of data.

In spite of this inability to make the rules quantitative at present, we hope in this paper to show that the principle of hard and soft acids and bases is extremely useful. We will take the area of organic chemistry for which a wealth of data exists for which little correlation has been done in terms of hardness and softness concepts.<sup>7</sup> It will turn out that much, but not all, of what we have to say has been noted before and explained in various ways. We wish to show an underlying pattern in all of these phenomena.

It should be stressed that the HSAB principle is not a theory but is a statement about experimental facts. Accordingly an explanation of some observation in terms of hard and soft behavior does not invalidate some other, theoretical explanation. In fact, the various theories which have been put forward<sup>2</sup> to explain the principles of hard and soft acids and bases in general usually include the previous explanations for the particular cases to be discussed in this paper.

### Thermodynamic Examples

We will first show how the thermodynamic stabilities of many kinds of organic molecules can be rationalized by the hard-soft concept. This leads to a better understanding of many well-known facts and to a prediction of some results that are probably not well known to most organic chemists.

The method that is used is to mentally break down an organic species into a Lewis acid fragment such as a carbonium ion or acylium ion, and a base fragment such as a carbanion, a hydride ion, or a halide ion. The stability of the molecule is then considered in terms of the acid-base interaction



When the acceptor atom of A is carbon, we are talking about what Parker has called carbon basicity.<sup>8</sup> An important paper by Hine and Weimar<sup>9</sup> has recently discussed this subject in a different way.

Some extended results from this paper may be conveniently used to introduce the subject. Table II shows the calculated equilibrium constants<sup>9</sup> for the gas phase reactions



It may be noted that when HB is a neutral molecule, the equilibrium constants in aqueous solution are not

(7) (a) A recent book by R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, uses the ideas of hard and soft to explain substitution reactions of organophosphorus compounds. (b) B. Saville, *Chem. Eng. News*, 43, 100 (May 31, 1965); *Angew. Chem.*, in press, has used the concept to discuss catalyzed reactions of organic chemistry.

(8) A. J. Parker, *Proc. Chem. Soc.*, 371 (1961).

(9) J. Hine and R. D. Weimar, Jr., *J. Am. Chem. Soc.*, 87, 3387 (1965).

Table II. Equilibrium Constants at 25°,  $K_{eq}$ , for the Reaction  $HB(g) + CH_3OH(g) \rightleftharpoons CH_3B(g) + H_2O(g)$ 

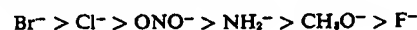
B	$K_{eq}^b$	$K_a$
H <sup>-</sup>	$1 \times 10^{11}$	$10^{-29}$ <sup>c</sup>
CN <sup>-</sup>	$3 \times 10^{14}$	$7 \times 10^{-10}$
CH <sub>3</sub> COCH <sub>2</sub> <sup>-</sup>	$2 \times 10^{11}$	$10^{-20}$
CH <sub>3</sub> S <sup>-</sup>	$2 \times 10^9$	$5 \times 10^{-11}$
CH <sub>3</sub> I <sup>-</sup>	$3 \times 10^9$	$10^{-40}$ <sup>c</sup>
I <sup>-</sup>	$2 \times 10^9$	$10^{+6}$
SH <sup>-</sup>	$3 \times 10^7$	$1 \times 10^{-7}$
Br <sup>-</sup>	$1 \times 10^7$	$10^9$
N <sub>2</sub> H <sub>2</sub> <sup>-</sup>	$6 \times 10^6$	$1 \times 10^{-6}$
Cl <sup>-</sup>	$3 \times 10^5$	$10^7$
NO <sub>2</sub> <sup>-</sup> <sup>c</sup>	$\sim 10^4$	$5 \times 10^{-4}$
NH <sub>2</sub> <sup>-</sup>	$8 \times 10^3$	$10^{-14}$ <sup>c</sup>
C <sub>6</sub> H <sub>5</sub> O <sup>-</sup>	$3 \times 10^3$	$1 \times 10^{-10}$
CH <sub>3</sub> O <sup>-</sup>	$3 \times 10^3$	$10^{-15}$
F <sup>-</sup>	$\sim 10^{-3}$	$1.4 \times 10^{-3}$

<sup>a</sup> Bonding to O in each case. CH<sub>3</sub>NO<sub>2</sub> is about 1.5 kcal more stable than CH<sub>3</sub>ONO. <sup>b</sup> Values of  $K_{eq}$  are from ref 9, except for B = NH<sub>2</sub><sup>-</sup>, N<sub>2</sub>H<sub>2</sub><sup>-</sup>, NO<sub>2</sub><sup>-</sup>, CH<sub>3</sub><sup>-</sup>, and F<sup>-</sup>. See ref 13, 16, and 31 for data; also Technical Notes 270-1 and 270-2, National Bureau of Standards, 1965-1966. <sup>c</sup> Estimated. See F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1958, p 344. <sup>d</sup> Estimated from  $K_a$  of aniline, phenol, and water. See F. G. Bordwell, "Organic Chemistry," The Macmillan Co., New York, N. Y., 1963, p 867.

different from those in the gas phase by more than a factor of 25 or so for reaction 4. Also the value of  $\Delta H^\circ$  is not different from the value of  $\Delta G^\circ$ , in the gas, by more than a kilocalorie or two. Since we will be discussing large differences, it will be possible to get data reasonably comparable to that in Table II by just knowing gas phase or aqueous heats of formation.

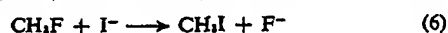
It can be seen that the equilibrium constant for reaction 4 is very large for bases such as CH<sub>3</sub><sup>-</sup>, I<sup>-</sup>, CH<sub>3</sub>S<sup>-</sup>, and H<sup>-</sup> which are listed as soft bases in Table I. For hard bases such as CH<sub>3</sub>O<sup>-</sup> and C<sub>6</sub>H<sub>5</sub>O<sup>-</sup>, the equilibrium constant is much smaller, and, for F<sup>-</sup>, the constant is less than unity. The immediate conclusion is that the methyl carbonium ion is a softer acid than is the proton which is a hard acid. Note that a large equilibrium constant for eq 4 does not mean that CH<sub>3</sub><sup>+</sup> is a stronger acid than H<sup>+</sup> in an intrinsic sense. It means only that CH<sub>3</sub><sup>+</sup> prefers the soft base and H<sup>+</sup> prefers the hard base in a competition of the type given by eq 2. It will be shown in the Appendix that H<sup>+</sup> is intrinsically a much stronger Lewis acid than CH<sub>3</sub><sup>+</sup>. There is obviously no correlation between the equilibrium constants for eq 4 and the strength of the bases toward the proton in water. The  $K_a$  values for the conjugate acids are given in Table II for each base. Some of these are only estimated values.

The equilibrium constants form an order of decreasing softness as follows.



Where the bases are the same, the order is quite similar to, but not identical with, those for  $\text{CH}_3\text{Hg}^+$ .

The criteria for class b, or soft, behavior are given by displacements such as



in protic solvents such as water or methanol. The data in ref 9 show that displacements such as eq 5 do occur, but just barely. Also literature data on eq 6 show that the equilibrium constant is slightly less than unity.<sup>10</sup> The data of Table II, however, show the very large increase in preference for  $\text{I}^-$  over  $\text{F}^-$  when  $\text{CH}_3^+$  is compared to the hard proton. The general conclusion is that the methyl carbonium ion is fairly soft but not as extremely soft as  $\text{CH}_3\text{Hg}^+$ , for example. It may be considered as a borderline case.

We can now make the prediction that displacements such as



will occur. The reactions will be relatively independent of the solvent. These are not trivial predictions since amines are always stronger bases (toward the proton) than their corresponding phosphines. One normally accepts the idea that the stronger base is bound more tightly. The concept of soft bases being bound more by the soft methyl carbonium ion produces the opposite prediction.

The heat of reaction 7 is  $-24.7$  kcal/mole so that it goes as predicted. The corresponding reactions in which  $\text{AsH}_3$  and  $\text{SbH}_3$  are converted to  $(\text{CH}_3)_3\text{As}$  and  $(\text{CH}_3)_3\text{Sb}$  by reaction with  $(\text{CH}_3)_3\text{N}$  are also strongly favored.<sup>11</sup> It is also of interest that a number of displacements of the kind shown in eq 8 can be carried out.<sup>12</sup>

An important point is what happens to the hardness or softness of a carbonium ion as its composition is varied. As an extreme case, we may go to the acylium ion,  $\text{CH}_3\text{CO}^+$ . Table III shows some equilibrium data for the exchange reaction



These were calculated from heats of reaction only. The entropy changes will be small and would not change the conclusions that may be drawn. Some equilibrium constants for reaction 9 in aqueous solution are also available and show the same behavior.<sup>9</sup>

We see that in  $\text{CH}_3\text{CO}^+$  the great preference that  $\text{CH}_3^+$  showed for soft bases has vanished. The equilibrium constant except for alkoxide and amide are less than unity. This simply means that the acylium ion prefers  $\text{OH}^-$  as a base even more than the proton does. It is a hard Lewis acid. Table III includes the  $\Delta pK_{\text{eq}}$  for reaction 9 and reaction 4. These numbers also give a pattern of decreasing softness from  $\text{H}^-$  to  $\text{NH}_3^-$ .

It is not surprising that the acylium ion is much harder than an alkyl carbonium ion. The electronega-

Table III. Equilibrium Constants at  $25^\circ$ ,  $K_{\text{eq}}$ , for the Reaction  $\text{CH}_3\text{COOH}(\text{g}) + \text{HB}(\text{g}) \rightleftharpoons \text{CH}_3\text{COB}(\text{g}) + \text{H}_2\text{O}(\text{g})$

B	$K_{\text{eq}}^a$	$\Delta pK_{\text{eq}}$
$\text{H}^-$	$10^{-8}$	26
$\text{I}^-$	$10^{-13}$	23
$\text{CH}_3\text{COCH}_2^-$	$10^{-10}$	21
$\text{CH}_3^-$	$10^{-9}$	17
$\text{SH}^-$	$10^{-6}$	13
$\text{Cl}^-$	$10^{-8}$	11
$\text{F}^-$	$10^{-5}$	5
$\text{CH}_3\text{O}^-$	1	3
$\text{NH}_3^-$	$10^4$	0

<sup>a</sup> Calculated from heats of formation only, ignoring the small entropy changes. Data from ref 13 and 14, except for  $\text{CH}_3\text{COCH}_2^-$  which is from J. L. Wood and M. M. Jones, *Inorg. Chem.*, 3, 1553 (1964).

tive oxygen atom would withdraw charge from the carbon making it a more positive center. In the same way we would expect  $\text{CF}_3^+$  to be harder than  $\text{CH}_3^+$ . This can be verified by examining the reaction<sup>13</sup>



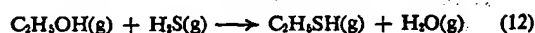
$$\Delta H^\circ = -18 \text{ kcal/mole at } 25^\circ$$

Thus  $\text{CF}_3^+$  prefers to bind  $\text{F}^-$  and  $\text{CH}_3^+$  prefers to bind  $\text{I}^-$  which justifies the statement that  $\text{CF}_3^+$  is harder than  $\text{CH}_3^+$ .

The effect of replacing H atoms by alkyl groups in the methyl carbonium ion gives an unexpected result. Consider the sequence of reactions<sup>14</sup>



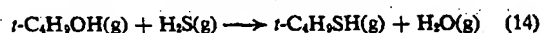
$$\Delta H^\circ = -10.4 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = -7.8 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = -5.8 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = -4.2 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = -3.2 \text{ kcal/mole at } 25^\circ$$

The conclusion is that replacing H atoms in  $\text{CH}_3^+$  by methyl groups leads to a progressively harder carbonium ion. Thus  $(\text{CH}_3)_3\text{C}^+$  is harder than  $\text{CH}_3^+$ .

This result is unexpected because the usual concept of an alkyl group is that it is electron releasing with respect to hydrogen. In fact the reverse must be true. Carbon is a more electronegative element than hydrogen.<sup>15</sup> Replacing H by  $\text{CH}_3$ , or other alkyl group, must result in a small removal of negative charge from the carbon atom of  $\text{CH}_3^+$ . Hence it becomes harder. It is also quite reasonable that  $\text{C}_6\text{H}_5^+$  is harder than  $\text{CH}_3^+$  since H atoms have been replaced by C atoms. We also note that  $\text{sp}^2$  carbon is more electronegative than  $\text{sp}^3$  carbon.<sup>15</sup>

(13) Heats of formation are from S. W. Benson, *J. Chem. Educ.*, 502 (1965), and estimates of P. G. Maslov and Yu. P. Maslov, *Khim. i Tekhnol. Topliv i Masel*, 3, 50 (1958); *Chem. Abstr.*, 53, 1910 (1958).

(14) Heats of formation of oxygenated compounds from J. H. S. Green, *Quart. Rev.* (London), 15, 125 (1961); of sulfur compounds, H. Mackle and P. A. G. O'Hare, *Tetrahedron*, 19, 961 (1963).

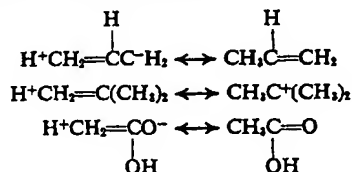
(15) The group electronegativity of  $\text{CH}_3$  is given as 2.30 compared to 2.20 for H. See H. J. Hinze, M. A. Whitehead, and H. H. Jaffé, *J. Am. Chem. Soc.*, 85, 148 (1963).

(10) R. H. Bathgate and E. A. Moelwyn-Hughes, *J. Chem. Soc.*, 3642 (1959); A. J. Parker, *ibid.*, 1328 (1961).

(11) S. B. Hartley, *et al.*, *Quart. Rev.* (London), 17, 204 (1963); L. H. Long and J. F. Sackman, *Trans. Faraday Soc.*, 51, 1062 (1955); 52, 1201 (1956); F. D. Rossini, *et al.*, National Bureau of Standards Circular 500, U. S. Government Printing Office, Washington, D. C., 1952.

(12) H. Hellman and O. Schumacher, *Ann. Chem.*, 640, 79 (1961).

It has recently been experimentally demonstrated by Laurie and Muentner<sup>16</sup> that a methyl group bonded to saturated carbon is electron withdrawing with respect to hydrogen. This is a pure inductive effect. The common belief that an alkyl group is electron donating with respect to hydrogen is largely based on examples in which an unsaturated carbon is involved. In such cases hyperconjugation will be important and an alkyl group can become a net electron donor. Examples would be (see also the Appendix)



A number of interesting correlations can now be made with the knowledge that hardness decreases in the order



For example<sup>17</sup>



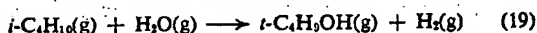
$$\Delta H^\circ = 27.6 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 21.8 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 17.2 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 15.4 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 14.9 \text{ kcal/mole at } 25^\circ$$

The increasing tendency for these reactions to occur can be neatly correlated with the fact that hard acids prefer to coordinate to  $\text{OH}^-$  and soft acids prefer  $\text{H}^-$ . Isomerizations, such as



$$\Delta H^\circ = -7.0 \text{ kcal/mole at } 25^\circ$$

find a ready explanation. Further examples will be given under the next heading.

### Symbiosis

Jørgensen<sup>18</sup> has pointed out that a common phenomenon occurs in coordination chemistry: soft ligands, or bases, tend to flock together on a central metal atom, and hard ligands tend to flock together. This mutual stabilizing effect was called symbiosis. The same symbiotic phenomenon occurs in organic chemistry. It was first pointed out by Hine,<sup>19</sup> who showed that C-F and C-O bonds in the same molecule tend to reinforce each other. Fluorine and oxygen being hard, and hydrogen (as hydride ion) being soft, the replacement of one hydrogen by F or O would make it easier for the next to be replaced. The reason for

(16) V. W. Laurie and J. S. Muentner, *J. Am. Chem. Soc.*, **88**, 2883 (1966).

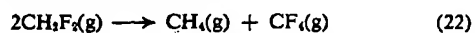
(17) Heats of formation of hydrocarbons from F. D. Rossini, *et al.*, "Selected Values of Physical and Thermodynamic Properties," Carnegie Press, Pittsburgh, Pa., 1953.

(18) C. K. Jørgensen, *Inorg. Chem.*, **3**, 1201 (1964).

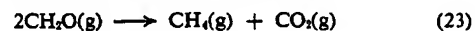
(19) J. Hine, *J. Am. Chem. Soc.*, **85**, 3239 (1963).

this has already been given in discussing why  $\text{CH}_3\text{CO}^+$  and  $\text{CF}_3^+$  are harder than  $\text{CH}_3^+$ . Thus piling up soft bases on an acceptor atom makes it soft, and piling up hard bases on an acceptor atom makes it hard. An outstanding example would be  $\text{BH}_3$ , which is a soft acid, and  $\text{BF}_3$ , which is a hard acid.

The least stable combinations would be mixtures of hard and soft ligands on one center. This is in agreement with the following cases.

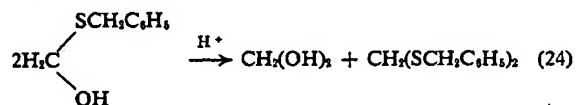


$$\Delta H^\circ = -26 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = -56.5 \text{ kcal/mole at } 25^\circ$$

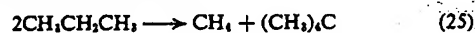
While thermodynamic data are not available, it is known<sup>20</sup> that the hemithioformal is unstable with



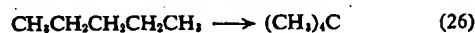
respect to disproportionation. A trace of acid is necessary to catalyze the conversion.

More quantitative data<sup>20b</sup> show that it is always more difficult to replace one OR group with SR in  $\text{R}'_2\text{C}(\text{OR})_2$  compounds than in  $\text{R}'_2\text{C}(\text{OR})\text{COR}$  compounds, thus the two oxygen atoms together have a symbiotic stabilizing effect. Equally well one can say that the carbonium ion  $\text{ROR}'_2\text{C}^+$  is harder than  $\text{R}'_2\text{C}^+$ .

An interesting example of symbiosis is found by comparing an alkyl group as a base, such as  $\text{CH}_3^-$ , with the  $\text{H}^-$  ion. Tables II and III show that  $\text{H}^-$  is softer than  $\text{CH}_3^-$ . Therefore, the most stable hydrocarbons should contain carbon atoms with the maximum number of C-H bonds or the maximum number of C-C bonds. The poorest combination has equal numbers of bonds to C and H for each carbon. We can predict the direction of the following reactions.



$$\Delta H^\circ = -8.0 \text{ kcal/mole at } 25^\circ$$



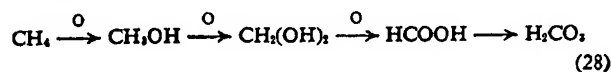
$$\Delta H^\circ = -4.7 \text{ kcal/mole at } 25^\circ$$

We have by this rule a simple explanation for the extra stability of highly branched hydrocarbons. As we mentioned earlier, explaining something by the concept of hard and soft acids and bases does not necessarily invalidate other, theoretical explanations of the same thing.

There are some limits to the concept of symbiosis. Reaction 27 (*cf.* eq 10) is endothermic by 50 kcal



because of the very positive heat of formation of  $\text{Cl}_4$ .<sup>18</sup> Presumably, steric strain in this molecule overcomes any symbiotic effects. Also in the successive oxidation of methane, the exothermicity increases in



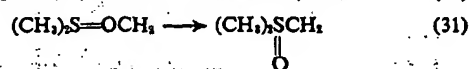
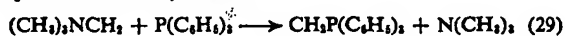
(20) (a) H. Böhme and H. P. Teltz, *Ann. Chem.*, **620**, 1 (1959); (b) see also W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 104 (1964); G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966).

each step, until the last. The probable explanation is that the acid  $\text{HOCO}^+$  is much stronger than any of its predecessors. Since  $\text{H}^-$  is also much stronger than  $\text{OH}^-$ , there is a larger reluctance for  $\text{HCOOH}$  to become  $\text{HOCO}^+$  than expected.

### Carbenes

A consideration of carbenes as Lewis acids illustrates the way in which the idea of hard and soft acids and bases can relate information from one area to another. Singlet states of carbenes are, of course, Lewis acids and should react as such. Bond formation to bases will also drive ground triplet states to excited singlet states. Simple considerations make it clear that  $\text{CH}_2$  should be a softer Lewis acid than  $\text{CH}_3^+$ , which is already fairly soft.

We immediately can understand the greater stability of phosphine compared to amine ylides, and of sulfide compared to oxide ylides.<sup>21</sup>



The instability of O ylides may help explain why the reaction



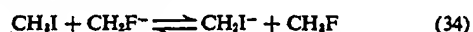
appears to go by an  $\text{S}_{\text{N}}1$  mechanism rather than by an  $\text{S}_{\text{N}}2$  mechanism with water acting as the nucleophile.<sup>22</sup>

The reverse of reaction 32 occurs readily. The rate at which various anions trap dichlorocarbene is given by the expected sequence  $\text{I}^- \sim \text{Br}^- > \text{Cl}^- > \text{F}^-$ ,  $\text{NO}_3^-$ ,  $\text{ClO}_4^-$ .<sup>23</sup> We can predict that the following equilibrium will lie well to the right.



The  $\text{CH}_2\text{I}^-$  is to be regarded as an acid-base complex of the soft acid  $\text{CH}_2$  and the soft base  $\text{I}^-$ .

More important, since  $\text{CH}_3^+$  is harder than  $\text{CH}_2$ , we can predict that the equilibrium



will also lie to the right. This result is unexpected since it says that an iodine atom is more acid strengthening than a fluorine atom, when attached to the carbon which loses the proton. Classical organic theory predicts just the opposite, the inductive effect of F being assumed greater than that of I.<sup>24</sup>

The data on the effect of halogen substituents on carbanion stability are somewhat incomplete. What there are seem to support the acid strengthening order  $\text{I} > \text{Br} > \text{Cl} > \text{F}$ . Using deuterium exchange as a measure of acidity, Hine found this order for various haloforms, pure and mixed.<sup>25</sup> Bell found  $\text{Br} > \text{Cl}$  for bromoacetone and chloroacetone from the rates of enolization.<sup>26</sup>

(21) W. Kirmse, "Carbene Chemistry," Vol. I, Academic Press Inc., New York, N. Y., 1964.

(22) W. J. Le Noble, *J. Am. Chem. Soc.*, **87**, 2434 (1965).

(23) J. Hine and A. M. Dowell, *ibid.*, **76**, 2688 (1954).

(24) G. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, Chapter 6.

(25) J. Hine, *et al.*, *J. Am. Chem. Soc.*, **79**, 1406 (1957); **80**, 819 (1958).

(26) R. P. Bell, E. Gelles, and E. Möller, *Proc. Roy. Soc. (London)*, **A198**, 310 (1949); R. P. Bell and O. M. Lidwell, *ibid.*, **A176**, 88 (1940).

More clear-cut results are found for the predictions



It is well established<sup>27</sup> that SR is more acid strengthening than OR, and  $\text{PR}_3$  is more acid strengthening than  $\text{NR}_3$ . The factors are as large as  $10^4$ .

It is pertinent to ask whether the replacement of a hydrogen atom by a halogen atom should increase acid strength at all, since  $\text{H}^-$  is very soft and  $\text{CH}_2$  is a soft acid. Consider the equilibrium



This must lie to the left since  $\text{CH}_3^+$  is a much stronger acid than  $\text{CH}_2$ , and  $\text{H}^-$  is a much stronger base than  $\text{F}^-$ . The tendency for the strongest acid to combine with the strongest base, in this case, will outweigh any considerations due to hardness or softness. In the important case of an alkyl substituent



equilibrium will lie to the right since  $\text{H}^-$  is both a somewhat weaker base and a somewhat softer base than  $\text{CH}_3^-$ . Thus,  $\text{CH}_2$  will coordinate with  $\text{H}^-$  and  $\text{CH}_3^+$  with  $\text{CH}_3^-$ .

A criterion for soft acids that may be used in the absence of other data is the formation of fairly stable complexes with special soft bases, such as carbon monoxide, olefins, and aromatics.<sup>2</sup> Carbenes are well known to form complexes with these bases.<sup>21</sup> It is likely that  $\pi$  complexes are formed with olefins and aromatic molecules, prior to more extensive reaction.<sup>28</sup> Carbene also forms a complex with soft metal atoms, another characteristic of soft Lewis acids.<sup>29</sup>

### Meaning of Stability

A great deal of confusion can arise when the term stable is applied to a chemical compound. One must specify whether it is thermodynamic or kinetic stability which is meant, stability to heat, to hydrolysis, etc. The situation is even worse when a rule such as the principle of hard and soft acids is used. The rule implies that there is an extra stabilization of complexes formed from a hard acid and a hard base, or a soft acid and a soft base. It still says very little about stability in an absolute sense. It is quite possible for a compound formed from a hard acid and a soft base to be more stable than one made from a better matched pair. All that is needed is that the first acid and base both be quite strong, say  $\text{H}^+$  and  $\text{H}^-$  combined to form  $\text{H}_2$ .

Frequently the rule can be used in a comparative sense, to say that one compound is more stable than another. Here also caution is required in order to make a meaningful statement. We will try to give some illustrations of how the principle can be usefully applied.

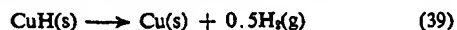
Consider the pair of compounds, NaH and CuH. The sodium ion is a hard Lewis acid; the cuprous ion is soft. Since hydride ion is also soft, the natural statement to make is that CuH is more stable than NaH. This clashes with the fact that sodium hydride is a well-known, apparently stable substance, and copper hy-

(27) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 71 ff.

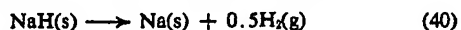
(28) G. A. Russell and D. G. Hendry, *J. Org. Chem.*, **28**, 1933 (1963).

(29) F. D. Mango and I. Dvoretzky, *J. Am. Chem. Soc.*, **88**, 1654 (1966).

dride is a little known, apparently very unstable substance. Actually the heat of formation of NaH is negative, while that of CuH is positive.<sup>30</sup> The latter compound is indeed unstable with respect to its elements and is hard to prepare and harder to keep.



$$\Delta H^\circ = -7.9 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 13.7 \text{ kcal/mole at } 25^\circ$$

The statement about stability based on the hard and soft concept does have meaning in spite of this. It is necessary, however, that an acid-base reaction be chosen as a reference, rather than the oxidation-reduction of eq 39 and 40. Hydrolysis is a good example.<sup>31</sup>



$$\Delta H^\circ = -43.6 \text{ kcal/mole at } 25^\circ$$



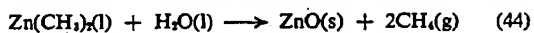
$$\Delta H^\circ = 5.2 \text{ kcal/mole at } 25^\circ$$

The heats show how readily  $\text{Na}^+$  coordinates with  $\text{H}_2\text{O}$ , compared to coordinating with  $\text{H}^-$ , whereas  $\text{Cu}^+$  prefers  $\text{H}^-$  to  $\text{H}_2\text{O}$ .

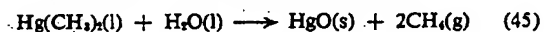
The same situation exists for organometallic compounds.  $\text{Al}(\text{CH}_3)_3$ ,  $\text{Zn}(\text{CH}_3)_2$ , and  $\text{Hg}(\text{CH}_3)_2$  are decreasingly less stable toward decomposition into their elements. Toward hydrolysis the opposite pattern is found.<sup>32</sup>



$$\Delta H^\circ/6 = -38 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ/2 = -22.5 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ/2 = 14 \text{ kcal/mole at } 25^\circ$$

This hydrolytic behavior is consistent with increasing softness of the Lewis acids  $\text{Al}^{3+} < \text{Zn}^{2+} < \text{Hg}^{2+}$ .

Another confusing situation arises when a molecule can be looked at in two or more ways, as far as considering it as an acid-base complex. This is almost always possible in organic chemistry. For example, methane may be considered as  $\text{H}^+\text{CH}_3^-$  or  $\text{CH}_3^+\text{H}^-$ . In the first case we have a hard-soft combination, in the second case a soft-soft combination. Is methane to be considered as unstable or stable? The answer is, of course, that a particular acid-base reaction must first be selected. This, in turn, will dictate the necessary formulation for methane. Two possible cases might be



$$\Delta H^\circ = 22 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = -12 \text{ kcal/mole at } 25^\circ$$

The first case considers  $\text{CH}_4$  as  $\text{CH}_3^+\text{H}^-$ , a soft-soft

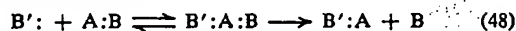
combination. The second case considers it to be  $\text{H}^+\text{CH}_3^-$  a hard-soft combination. The other acid-base combinations are also indicated in eq 46 and 47.

### Kinetic Applications

The principle of hard and soft acids and bases may also be applied to the rates of nucleophilic and electrophilic substitution reactions. A paper on nucleophilic reactivity was indeed the first to call attention to those properties which were later labeled hard and soft.<sup>33</sup> It was noted that electrophilic centers such as  $\text{RCO}^+$ ,  $\text{H}^+$ ,  $\text{RSO}_2^+$ ,  $(\text{RO})_2\text{PO}^+$ , and  $(\text{RO})_2\text{B}^+$  reacted rapidly with nucleophiles which were strongly basic to the proton and not very polarizable, such as  $\text{OH}^-$  and  $\text{F}^-$ . Other electrophilic centers such as  $\text{RCH}_2^+$ ,  $\text{R}_2\text{P}^+$ ,  $\text{RS}^+$ ,  $\text{Br}^+$ ,  $\text{R}_2\text{N}^+$ ,  $\text{RO}^+$ , and  $\text{Pt}^{2+}$  reacted rapidly with highly polarizable nucleophiles such as  $\text{I}^-$  and  $\text{R}_3\text{P}$ .

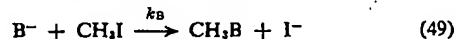
The general rule can easily be stated: hard electrophilic centers (acids) react rapidly with hard nucleophiles (bases), and soft electrophilic centers react rapidly with soft nucleophiles. The rule refers to  $\text{SN}2$ - or  $\text{SE}2$ -type mechanisms. An additional corollary can also be stated: softness is more important in rate phenomena than in thermodynamic phenomena. That is, a medium soft acid, such as  $\text{CH}_3^+$ , will be even more reactive to soft bases than the stability of the products would predict. This rule follows partly from experimental observations and partly from the theories which explain preferential hard-hard and soft-soft interactions.<sup>2</sup>

In an  $\text{SN}2$  or  $\text{SN}2(\text{lim})$  mechanism the rate depends as usual on the difference in free energy of the transition state and the reactants



The transition state, in  $\text{B}':\text{A}:\text{B}$ , is just another acid-base complex with an increased coordination number for the electrophilic atom A and somewhat longer bonds. The same considerations that predict the stability of acid-base complexes in general should predict rates of reaction. The increased coordination number in  $\text{B}':\text{A}:\text{B}$  puts an increased negative charge on A and makes it softer. Hence softness in  $\text{B}'$  is more helpful than for equilibria only.

Table IV shows a partial listing of relative nucleophilic reactivities toward methyl iodide in methanol solvent at  $25^\circ$ . The data are given in terms of a



parameter  $n^\circ_{\text{CH}_3\text{I}}$  patterned after that of Swain and Scott,<sup>34</sup> who used  $\text{CH}_3\text{Br}$  as a reference compound and water as a solvent. The rate constant for methanol,  $k_B$ , has been converted to second-order units. That is, the first-order rate constant for methanolysis has been divided by  $26 \text{ M}$ .

$$n^\circ_{\text{CH}_3\text{I}} = \log(k_B/k_S) \quad (50)$$

There is a range of nucleophilic reactivity covering nearly  $10^{10}$ . The important feature for the present purpose is that the reactivities do not parallel the basicities toward the proton, a hard reference acid, as given by the  $\text{pK}_a$  values shown in the table. Also im-

(30) I. C. Warf, *J. Inorg. Nucl. Chem.*, **28**, 1031 (1966).

(31) Heats of formation of aqueous ions from F. D. Rossini, *et al.*, ref 11.

(32) Heats of formation from ref 31 and from L. H. Long and R. G. W. Norrish, *Phil. Trans., Roy. Soc. London, Ser. A*, **241**, 587 (1949).

(33) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

(34) C. G. Swain and C. B. Scott, *ibid.*, **75**, 141 (1953).



Table IV. Nucleophilic Reactivity Parameters for Reaction with Methyl Iodide in Methanol at 25°

B	$n^\circ \text{CH}_3\text{I}^a$	$pK_a$
$\text{CH}_3\text{OH}$	0.00	$\sim 0$
$\text{Cl}^-$	4.37	-7
$(\text{CH}_3)_2\text{S}$	5.34	-5.3
$\text{NH}_3$	5.50	9.2
$\text{C}_2\text{H}_5\text{O}^-$	5.79	9.9
$\text{Br}^-$	5.79	-9
$\text{CH}_3\text{O}^-$	6.29	16
$(\text{CH}_3)_2\text{Se}$	6.32	...
$\text{CN}^-$	6.70	9.1
$(\text{C}_2\text{H}_5)_3\text{As}$	7.10	2
$\text{I}^-$	7.42	-9.5
$(\text{C}_2\text{H}_5)_3\text{P}$	8.72	8.9
$\text{C}_2\text{H}_5\text{S}^-$	9.92	6.5

<sup>a</sup>  $n^\circ \text{CH}_3\text{I} = \log(k_8/k_8)$  where  $k_8$  is in second-order units. Data from J. Songstad, to be published in detail.

portant are the reactivity sequences  $\text{I}^- > \text{Br}^- > \text{Cl}^-$ ,  $\text{R}_2\text{Se} > \text{R}_2\text{S} > \text{ROH}$ , and  $\text{R}_3\text{P} > \text{R}_3\text{As} > \text{R}_3\text{N}$ . This is typical soft behavior. Furthermore the increased reactivity of the more polarizable nucleophiles is greater than the increased stability of the products, particularly for the halide ions.

Series such as those of Table IV are very sensitive to the solvent, as Parker particularly has emphasized.<sup>35</sup> The reactivity order for the halide ions can be inverted by switching to a dipolar aprotic solvent, such as dimethylformamide. The equilibrium constants are also drastically changed in the same direction. This does not mean that the high reactivity of polarizable reagents is an accident due to a peculiar choice of solvents.

First of all, it is only anions that are seriously affected by changing solvents.<sup>2</sup> If one stays with neutral reagents, the order remains unchanged on switching from protic to dipolar aprotic solvents. For example, the reactivity of phosphines toward ethyl iodide is essentially the same in the solvents methanol, acetone, and nitromethane.<sup>36</sup> That is, the rates are unchanged on changing solvents, whereas halide ion reactivities change<sup>35</sup> by factors of 400 for  $\text{I}^-$  and  $3 \times 10^6$  for  $\text{Cl}^-$ . Also the rates of reaction of tertiary amines with alkyl iodides increase by less than a factor of ten in going from methanol to acetone or nitrobenzene.<sup>37</sup> It is obvious that the reactivity order  $\text{P} \gg \text{N}$  is maintained in all solvents used.

Secondly, the inversion in reactivity for the halides occurs only because  $\text{CH}_3^+$  is a borderline soft acid. If a more typically soft substrate, such as  $\text{Pt}^{2+}$ , is taken, the reactivity sequence  $\text{I}^- > \text{Br}^- > \text{Cl}^-$  is maintained even in dipolar aprotic solvents.<sup>38</sup> The spread in reactivity is reduced, as expected. Iodide ion is more reactive than chloride ion by a factor of  $10^4$  in methanol and by a factor of only 200 in acetone and dimethyl sulfoxide. Solvation effects, while important, are rather predictable perturbations of the basic pattern of nucleophilic reactivity.

The specific stabilization of small, basic anions by protic solvents is itself an example of the HSAB principle.<sup>2</sup> Hydrogen bonding is a hard acid-hard

base interaction. Hence the activity of  $\text{F}^-$  and  $\text{CH}_3\text{O}^-$  is reduced most in going from a solvent such as dimethyl sulfoxide to methyl alcohol. Dipolar aprotic solvents are to be considered as fairly soft compared to water and alcohol.

If the substrate taken is an acyl derivative such as an ester or an acyl halide, the pattern of nucleophilic reactivity is completely changed in line with the hardness of the carbonyl function,  $\text{RCO}^+$ . Except for the perturbation known as the *alpha effect*,<sup>39</sup> rates vary fairly regularly in accord with the proton basicity of the nucleophile.<sup>40</sup> Soft bases which are not also strong bases toward the proton, are quite ineffective. The Brønsted relationship often holds between the rate constant and  $K_a$  of the conjugate acid.<sup>40</sup>

The prediction can be made that alkyl halides such as *t*- $\text{C}_4\text{H}_9\text{Cl}$  and  $\text{CH}_3\text{OCH}_2\text{Cl}$  should be less sensitive to polarizability in the nucleophile than is  $\text{CH}_3\text{I}$  or  $\text{CH}_3\text{Cl}$ . This follows from the previous discussion that shows  $(\text{CH}_3)_2\text{C}^+$  and  $\text{HOCH}_2^+$  to be harder than  $\text{CH}_3^+$ . It is well known that sensitivity to the nature of the nucleophilic reagent decreases steadily in the series  $\text{CH}_3\text{X} > \text{C}_2\text{H}_5\text{X} > i\text{-C}_3\text{H}_7\text{X} > t\text{-C}_4\text{H}_9\text{X}$ . This includes sensitivity to the hard bases such as hydroxide ion and various oxygen donor solvents.<sup>42</sup> Nevertheless, in agreement with the above prediction, the falloff in relative rates in the series  $\text{CH}_3\text{X} > \text{C}_2\text{H}_5\text{X} > i\text{-C}_3\text{H}_7\text{X}$  is considerably greater for soft nucleophiles such as  $\text{S}_2\text{O}_3^{2-}$ ,  $\text{R}_3\text{P}$ , and  $\text{I}^-$  than for hard oxygen donor bases.<sup>43</sup>

There also are some interesting results from studies with ambident nucleophiles.<sup>44</sup> As pointed out earlier, such nucleophiles usually have one donor atom softer than the other.<sup>33</sup> The mode of action can then be predicted from the hardness or softness of the electrophilic substrate. In the case of thiocyanate ion we have



It is of interest that *t*- $\text{C}_4\text{H}_9\text{Cl}$  reacts with the hard oxygen atom of  $\text{NO}_2^-$ , while the softer  $\text{CH}_3\text{I}$  reacts with the softer nitrogen atom.<sup>44</sup> Also enolate ions react at the soft carbon atom with  $\text{CH}_3\text{I}$  and at the hard oxygen atom with  $\text{CH}_3\text{OCH}_2\text{Cl}$ .<sup>45</sup> Hudson has discussed a number of other reactions of ambident nucleophiles from the viewpoint of hardness and softness.<sup>46</sup> The expected results are usually found, though there are some ambiguous cases. The phosphonate anions,  $(\text{RO})_2\text{PO}^-$ , have a fairly soft center in the  $\text{P}^{\text{III}}$  atom and a hard center in the oxygen atom. Nevertheless, the

(39) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); W. P. Jencks and J. Carriulo, *J. Am. Chem. Soc.*, **82**, 1778 (1960); M. Green and R. F. Hudson, *J. Chem. Soc.*, 1055 (1962); T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, **86**, 418 (1964).

(40) A Brønsted relationship for a series of bases in which the donor atom is constant does not in itself prove that proton basicity is important. Substituents may be changing the electron density at the donor atom, making it harder or softer.<sup>41</sup>

(41) E. Thorsteinson and F. Basolo, *J. Am. Chem. Soc.*, **88**, 3929 (1966).

(42) See C. G. Swain, R. B. Mosely, and D. E. Brown, *ibid.*, **77**, 3731 (1955), for example.

(43) P. M. Dunbar and L. P. Hammett, *ibid.*, **72**, 109 (1950), for  $\text{S}_2\text{O}_3^{2-}$ ; ref 36 for  $\text{R}_3\text{P}$ ; and C. K. Ingold, *Quart. Rev. (London)*, **11**, 1 (1957), for  $\text{I}^-$  and  $\text{OR}^-$ .

(44) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffand, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

(45) J. L. Simonsen and R. Storey, *J. Chem. Soc.*, 95, 2106 (1909).

(46) Reference 7a, Chapter 4; R. F. Hudson, in "Organic Reaction Mechanisms," Special Publication No. 19, The Chemical Society, London, 1965, p 93 ff.

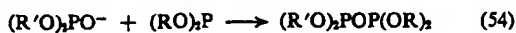
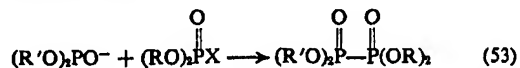
(35) A. J. Parker, *Quart. Rev. (London)*, **16**, 163 (1962); A. J. Parker, *et al.*, *J. Am. Chem. Soc.*, **88**, 1911 (1966); *J. Chem. Soc., Inorg.*, 152 (1966).

(36) W. A. Henderson, Jr., and S. A. Buckler, *J. Am. Chem. Soc.*, **82**, 5794 (1960).

(37) R. G. Pearson, *J. Chem. Phys.*, **20**, 1478 (1952).

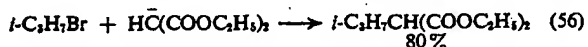
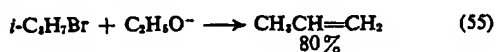
(38) U. Belluco, M. Martelli, and A. Orio, *Inorg. Chem.*, **5**, 592 (1966).

proton is known to bind exclusively to the phosphorus atom.<sup>47</sup> This atom is much more basic than the oxygen atom, even to hard Lewis acids. It is not too surprising that reactions such as



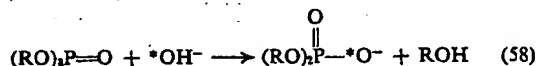
can both occur since opposing tendencies exist. With alkyl halides reaction normally occurs at the P atom.

An even more common case than that of ambident nucleophiles is that of molecules with multiple electrophilic centers. Most organic compounds fall into this category. Even as simple a molecule as  $CH_3Br$  has three centers, the C, H, and Br atoms. The HSAB principle can be of great value in understanding the mode of attack of various nucleophiles. For example, we have the following reactions of  $i\text{-C}_3\text{H}_7\text{Br}$ .<sup>48</sup>



The hard ethoxide ion attacks the proton, giving elimination, and the soft malonate anion attacks tetrahedral carbon with displacement of bromide ion. It should be noted that the proton basicities of the two anions are virtually identical.<sup>49</sup>

Similarly soft nucleophiles attack the alkyl group of phosphate esters while hydroxide ion and fluoride ion attack the hard phosphorus(V) site.<sup>50</sup> Many other examples can be thought of, some of which are discussed by Hudson.<sup>51</sup>



An extreme case is afforded by the  $\alpha$ -halo ketones, which present no less than five electrophilic sites. Hard bases attack the hard carbonyl carbon, or the proton. Medium soft bases, such as pyridine or  $\text{RS}^-$ , attack the tetrahedral carbon to give displacement. The softest bases such as  $\text{I}^-$  and  $\text{R}_3\text{P}$  will cause dehalogenation of iodo and bromo ketones. Recently nucleophilic attack at the oxygen atom of a halo ketone by an alkyl phosphite has also been demonstrated.<sup>52</sup> Note that the oxygen atom of a carbonyl group is a hard basic site, but is a soft acid site. The same situation is found in hydrogen peroxide, which is composed of soft  $\text{OH}^-$  combined with hard  $\text{OH}^+$ . Only soft bases will cause nucleophilic displacements at peroxide oxygen.<sup>53</sup>

Saville<sup>7b</sup> has used the HSAB principle as a guide for selecting catalysts in acid-base substitution reactions. He points out that the reactions of a hard-soft acid-base complex are the easiest to catalyze. The selection

(47) G. O. Doak and L. D. Freedman, *Chem. Rev.*, **61**, 31 (1961).

(48) F. G. Bordwell, "Organic Chemistry," The Macmillan Co., New York, N. Y., 1963, p 218.

(49) R. G. Pearson, *J. Am. Chem. Soc.*, **71**, 2212 (1949).

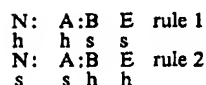
(50) D. C. Harper and R. F. Hudson, *J. Chem. Soc.*, 1356 (1958).

(51) See ref 46, also Chapter 7 of ref 7a; E. Hünig, *Angew. Chem. Intern. Ed. Engl.*, **3**, 548 (1964).

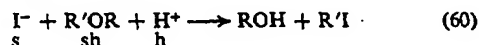
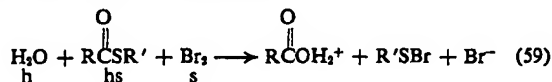
(52) B. Miller, *J. Am. Chem. Soc.*, **88**, 1814 (1966).

(53) J. O. Edwards, "Peroxide Reaction Mechanisms," Interscience Publishers, Inc., New York, N. Y., 1962.

of the catalyst is given by two rules depending on the substrate.

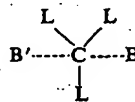


The selection of both the substituting reagent (E or N) and the nucleophilic or electrophilic catalyst (N or E) depends on a match of the hard or soft properties of each part of the acid-base complex. An illustrative case or two is self-explanatory.



### Symbiotic Effects on Rates

Inasmuch as the transition state for an  $\text{S}_\text{N}2$  reaction may be regarded as an acid-base complex, according to eq 48, there should be symbiotic effects on rates of nucleophilic displacement reactions. That is, a grouping on the central carbon atom should stabilize the transition state and cause an increased rate of reaction. The ligands include the entering and leaving group as well as the three groups, L, in the trigonal plane of the activated complex.



In fact just such an effect has been pointed out by Bunnett.<sup>54</sup> Large ratios for  $k_{\text{C}_6\text{H}_5\text{S}}/k_{\text{CH}_3\text{O}^-}$  and  $k_{\text{I}^-}/k_{\text{CH}_3\text{O}^-}$  are found when these reagents are B' and either B or L become progressively heavier halides. A number of other examples with other nucleophiles have also been listed.<sup>54,55</sup>

In the case of aromatic nucleophilic substitution, it is usually found that the rate ratio  $k_{\text{ArF}}/k_{\text{ArI}}$  is large for hard nucleophiles such as  $\text{CH}_3\text{O}^-$  and  $\text{N}_3^-$ , and low for soft nucleophiles such as  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{SCN}^-$ , and  $\text{C}_6\text{H}_5\text{S}^-$ . This is the predicted result. However,  $\text{CH}_3\text{S}^-$  is definitely anomalous in giving a large rate ratio.<sup>56</sup>

For displacements on tetrahedral carbon there is little doubt that the symbiotic effect is real and seems to be quite general. In order to avoid complications due to steric hindrance, it is best to consider only variations in B and B'. The rule is that higher rates are found when B and B' are both hard or both soft. It is usually necessary to look at ratios of rates to see the effect. It is also necessary to compare rates in the same, or similar solvents.

Tables V and VI show relative rate data for some organic halides. The general pattern is for higher rate ratios for the heavier halides as the softness of the nucleophile increases. The common statement<sup>57</sup> that

(54) J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5970 (1957).

(55) J. F. Bunnett and J. D. Reinheimer, *ibid.*, **84**, 3284 (1962); A. J. Sisti and S. Lowell, *J. Org. Chem.*, **29**, 1635 (1964).

(56) J. Miller and K. W. Wong, *J. Chem. Soc.*, 5454 (1965); K. C. Ho, J. Miller, and K. W. Wong, *ibid.*, **Org., 310 (1966).**

(57) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 339; A. Streitwieser, Jr., *Chem. Rev.*, **56**, 601 (1956).



Table V. Reactivity Ratios for Methyl Halides in Water at 25°  
 $\text{CH}_3\text{X} + \text{B}^- \rightarrow \text{CH}_3\text{B} + \text{X}^-$

Nucleophile, B	$k_{\text{CH}_3\text{I}}/k_{\text{CH}_3\text{Cl}}$	$k_{\text{CH}_3\text{I}}/k_{\text{CH}_3\text{Br}}$	Ref
$\text{H}_2\text{O}$	13	$1 \times 10^3$	a
$\text{F}^-$	5.5	...	b
$\text{OH}^-$	10	$1 \times 10^3$	a
$\text{Cl}^-$	...	$1 \times 10^3$	b,c
$\text{Br}^-$	86	...	b-d
$\text{I}^-$	24	$2.4 \times 10^4$	a,e
$\text{S}_2\text{O}_3^{2-}$	31	...	f

<sup>a</sup> I. Fells and E. A. Moelwyn-Hughes, *J. Chem. Soc.*, 398 (1959).  
<sup>b</sup> R. H. Bathgate and E. A. Moelwyn-Hughes, *ibid.*, 2647 (1959).  
<sup>c</sup> R. B. Fahim, Thesis, Cambridge, 1954; H. G. Holland, Thesis, Cambridge, 1954. <sup>d</sup> E. A. Moelwyn-Hughes, *J. Chem. Soc.*, 779 (1938). <sup>e</sup> E. R. Swart and H. LeRoux, *ibid.*, 409 (1957). <sup>f</sup> E. A. Moelwyn-Hughes, *Trans. Faraday Soc.*, 37, 279 (1941).

Table VI. Reactivity Ratios for Organic Halides at 25°

Reactants	Solvent	$k_{\text{Br}}/k_{\text{Cl}}$	$k_{\text{I}}/k_{\text{Cl}}$	Ref
$-\text{OCH}_2\text{CH}_2\text{X}$	$\text{H}_2\text{O}$	59	54	a
$\text{NH}_2\text{CH}_2\text{CH}_2\text{X}$	$\text{H}_2\text{O}$	70	...	b
$\text{C}_6\text{H}_5\text{CHSO}_2\text{CH}_2\text{CH}_2\text{X}$	$\text{CH}_3\text{OH}$	280	670	c
$\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{X} + \text{piperidine}$	$\text{CH}_3\text{OH}$	108	114	d
$\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{X} + \text{aniline}$	$\text{CH}_3\text{OH}-\text{H}_2\text{O}$	97	99	e
$\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{X} + \text{thiourea}$	$\text{CH}_3\text{OH}$	182	341	d

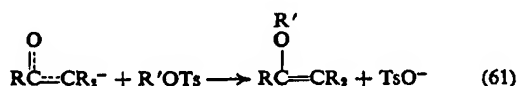
<sup>a</sup> C. L. McCabe and J. C. Warner, *J. Am. Chem. Soc.*, 70, 4031 (1948). <sup>b</sup> H. Freundlich and G. Salomon, *Z. Physik. Chem. (Leipzig)*, 166, 161 (1933). <sup>c</sup> J. M. Williams, Ph.D. Thesis, Northwestern University, Evanston, Ill., 1966. <sup>d</sup> W. T. Brannen, Ph.D. Thesis, Northwestern University, Evanston, Ill., 1962. <sup>e</sup> J. W. Baker, *J. Chem. Soc.*, 1148 (1932).

the relative reactivities for alkyl halides,  $\text{RCl}:\text{RBr}:\text{RI} = 1:50:100$ , is valid for alcohol, alkoxide ions, and amines in alcoholic solvents. When softer nucleophiles are used, the rate ratios may become very much larger, even in alcohol solvents.<sup>54,55</sup> In dipolar aprotic solvents, the ratios become higher still.<sup>55,56</sup>

Figure 1 shows a plot of Swain and Scott's  $n$  values<sup>54</sup> plotted against some  $n^\circ_{\text{CH}_3\text{I}}$  values defined in eq 50. Since the  $n$  values are defined in an analogous way except that  $\text{CH}_3\text{Br}$  is the substrate and water is the solvent, we could call them  $n^\circ_{\text{CH}_3\text{Br}}$  values to be consistent.

The slope of Figure 1 is 1.4. A slope greater than unity means that  $\text{CH}_3\text{I}$  reacts relatively faster with the better nucleophiles. These in turn are the softer nucleophiles, in general, so the prediction of a higher rate when both  $\text{B}'$  and  $\text{B}$  are very soft is borne out. A plot of  $n^\circ_{\text{CH}_3\text{I}}$  values in methanol against  $n^\circ_{\text{CH}_3\text{I}}$  values in water gives a slope very nearly equal to 1, perhaps 1.05. The solvent correction is accordingly small.

A comparison of tosylate or sulfate, which are hard, and bromide or iodide, which are soft, as leaving groups also shows the symbiotic effect. For instance, sulfates and tosylates react with enols to give largely O alkylation<sup>59</sup>



(58) B. O. Coniglio, *et al.*, *J. Chem. Soc., Org.*, 152 (1966).  
 (59) (a) G. J. Heizswolf and H. Kloosterziel, *Chem. Commun.*, 51 (1966); (b) W. S. Johnson, *et al.*, *J. Am. Chem. Soc.*, 84, 2181 (1962).

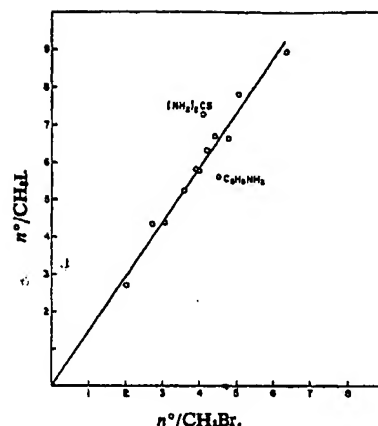


Figure 1. Relative reactivities toward  $\text{CH}_3\text{I}$  in methanol plotted against relative reactivities toward  $\text{CH}_3\text{Br}$  in water. Nucleophiles are (in ascending order)  $\text{CH}_3\text{OH}$  or  $\text{H}_2\text{O}$ ,  $\text{F}^-$ ,  $\text{OAc}^-$ ,  $\text{Cl}^-$ , pyridine, aniline,  $\text{N}_3^-$ ,  $\text{Br}^-$ ,  $\text{CH}_3\text{O}^-$  or  $\text{OH}^-$ ,  $\text{SCN}^-$ ,  $\text{CN}^-$ , thiourea,  $\text{I}^-$ , and  $\text{S}_2\text{O}_3^{2-}$ .

but bromides and iodides react to give largely C alkylation.<sup>60</sup>



The rate ratio for alkyl tosylates and alkyl bromides is a function of the nucleophilic reagent used. If a hard nucleophile is used, the ratio,  $k_{\text{OTs}}/k_{\text{Br}}$ , is large. If a soft nucleophile is used, the ratio is small. Some representative data are shown.<sup>61</sup>

$\text{C}_6\text{H}_5\text{X} \xrightarrow{\text{C}_2\text{H}_5\text{OH}} \text{C}_6\text{H}_5\text{OC}_2\text{H}_5$	$\text{S}_{\text{N}}2$	$k_{\text{TsO}}/k_{\text{Br}}$	15
$\text{CH}_3\text{X} \xrightarrow{\text{C}_2\text{H}_5\text{O}^-} \text{CH}_3\text{OC}_2\text{H}_5$	$\text{S}_{\text{N}}2$		5
$\text{CH}_3\text{X} \xrightarrow{\text{RS}^-} \text{CH}_3\text{SR}$	$\text{S}_{\text{N}}2$		0.3
$n\text{-C}_4\text{H}_9\text{X} \xrightarrow{\text{I}^-} n\text{-C}_4\text{H}_9\text{I}$	$\text{S}_{\text{N}}2$		0.3
$t\text{-C}_4\text{H}_9\text{X} \xrightarrow{\text{CH}_3\text{CN}} (\text{CH}_3)_2\text{C}=\text{CH}_2$	$\text{E}1$		2000
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{X} \xrightarrow{\text{C}_2\text{H}_5\text{O}^-} \text{C}_6\text{H}_5\text{CH}=\text{CH}_2$	$\text{E}2$		0.1

The low ratios for  $\text{RS}^-$  and  $\text{I}^-$  show the symbiotic stabilization of the transition state when the leaving group is bromide ion. The high ratios for  $\text{C}_2\text{H}_5\text{OH}$  and  $\text{C}_2\text{H}_5\text{O}^-$  show the same phenomenon when the leaving group is tosylate. The last two examples show a remarkable difference between an  $\text{E}1$  and an  $\text{E}2$  elimination. The low ratio in the latter case must be a consequence of the polarizable double bond (a soft base) being involved in the transition state.

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## Appendix

While it is not possible to set up an absolute order of acid strengths, it is meaningful to say that one Lewis acid is stronger than another for virtually every refer-

(60) Reference 57b; D. Caine, *J. Org. Chem.*, 29, 1868 (1964); G. Brieger and W. M. Pelletier, *Tetrahedron Letters*, 3553 (1965).  
 (61) H. M. R. Hoffman, *J. Chem. Soc.*, 6753, 6762 (1965).

ence base. This can be demonstrated by comparing the methyl carbonium ion with the proton. The heats of formation of  $H^+$  (367 kcal) and of  $CH_3^+$  (262 kcal) at 25° are needed.<sup>62</sup> We have the following gas phase reactions.



$$\Delta H^\circ = 87 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 104 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 115 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 100 \text{ kcal/mole at } 25^\circ$$

For the last equation we need the result that the proton affinity of methanol exceeds that of water by 15 kcal.<sup>63</sup>

- (62) D. D. Wagman, *et al.*, Technical Notes 270-1 and 270-2, National Bureau of Standards, Washington, D. C., Oct 1965, May 1966.  
 (63) M. S. B. Munson, *J. Am. Chem. Soc.*, **87**, 2305 (1965).



$$\Delta H^\circ = -15 \text{ kcal/mole at } 25^\circ$$

We have the result that  $H^+$  is a stronger acid than  $CH_3^+$  for all possible combinations of a strong, soft base ( $H^-$ ), a weak, soft base ( $I^-$ ), a strong, hard base ( $OH^-$ ), and a weak, hard base ( $H_2O$ ). These gas phase reactions are the best measure of intrinsic acid strength.

In passing, it may be noted that the effect of the methyl group, when replacing hydrogen, is to always increase the proton affinity of a base by about 15 kcal.<sup>63</sup> This is usually considered to be a base strengthening inductive effect, as in eq 67. It is more consistent to say that eq 67 is exothermic because  $H^+$ , which is strong, prefers  $OH^-$ , which is strong. The weaker  $CH_3^+$  is then left with the weaker base  $H_2O$ . In the same way  $CH_3NH_2$  is a stronger base than  $NH_3$ .



because  $H^+$  binds  $NH_3^-$  strongly and the  $CH_3^+$  is left with the weaker base  $NH_3$ . As mentioned earlier, the methyl group can be electron donating by hyperconjugation but appears to have an electron-withdrawing inductive effect.

## A Direct, Qualitative Determination of Nonchair and Distorted-Chair Conformations of Six-Membered Rings

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**Abstract:** The ratio ( $R$ ) of the average  $\nu_{trans}$  to the average  $\nu_{cis}$  in six-membered rings of the type I has been found to be nearly independent of the electronegativity of X and Y. Hence,  $R$  becomes a direct measure of conformational effects. For molecules that exist in the perfect-chair conformation,  $R$  is close to 2.0. Deviations from this value are taken to indicate the presence of distortions from the ideal chair. A number of nonchair and distorted-chair conformations have thus been detected and described. For molecules in the flexible family,  $R$  is approximately  $1.2 \pm 0.2$ . Certain deformations of the chair associated with the inclusion of sulfur or selenium atoms in the ring are characterized by  $R \geq 2.75$ . Although unsubstituted cyclohexanone assumes a slightly flattened chair ( $R = 1.7$ ), the 4,4-disubstituted derivatives may be in the flexible conformation.

Seventy-five years after Sachse's postulation<sup>1</sup> of the existence of the chair and boat forms of cyclohexane, the generally less favored boat family of conformations has achieved sufficient status to warrant extensive reviewing.<sup>2-5</sup> Three overlapping classes of "boat" forms may be enumerated: (1) compounds that are constrained to the boat conformation by geometrical considerations, such as bridging in norbornane, ring fusion in *trans,syn,trans*-perhydrophenanthrene, complexation in the piperazine-palladium chloride adduct,<sup>6</sup> or hydrogen bonding in  $\psi$ -tropine;<sup>7</sup> (2) ring

systems that assume the boat or twist-boat forms to relieve steric interactions of bulky substituents, as in *trans*-1,3-di-*t*-butylcyclohexane<sup>8</sup> and a number of steroids; and (3) molecules such as 1,4-cyclohexanedione<sup>9</sup> that appear to have an "inherent" preference for the boat family.<sup>10</sup> We shall be exclusively interested in the third class, which has become populated only recently. Membership in this group has generally been restricted to molecules containing more than one trigonally hybridized atom: 1,4-cyclohexanedione,<sup>8,9,11-13</sup>

(8) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960).

(9) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *ibid.*, **88**, 2999 (1966).

(10) By the "boat family" we mean the whole spectrum of "pseudo rotamers." A discussion of the various conformational arrangements is given in ref 5, pp 472-473. In the present context, we shall use the term "boat" for  $\theta = 0, 60$ , or  $120^\circ$ , "twist-boat" for  $\theta = 30, 90$ , or  $150^\circ$ , and "flexible form" or "boat family" to indicate the continuous conformational set of interconverting pseudo rotamers.

(11) P. Groth and O. Hassel, *Acta Chem. Scand.*, **18**, 923 (1964).

- (1) H. Sachse, *Ber.*, **23**, 1363 (1890).  
 (2) J. Levisalles, *Bull. Soc. Chim. France*, 551 (1960).  
 (3) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962).  
 (4) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965, p 275 ff.  
 (5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 469 ff.  
 (6) O. Hassel and B. F. Pedersen, *Proc. Chem. Soc.*, 394 (1960).  
 (7) G. Fodor and K. Nador, *Nature*, **169**, 462 (1952).

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